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UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF CALIFORNIA

IN RE: INCRETIN-BASED THERAPIES PRODUCTS LIABILITY LITIGATION

Case No. 13-md-2452-AJB-MDD

DEFENDANTS' REPLY IN SUPPORT OF THEIR MOTION FOR SUMMARY JUDGMENT BASED ON PREEMPTION

Date: October 20, 2020
Time: 9:00 AM
Courtroom: 4A
Judge: Hon. Anthony J. Battaglia
Magistrate: Hon. Mitchell D. Dembin

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

OTHER AUTHORITIES

INTRODUCTION

After years of discovery, three rounds of briefing, appeal, and the Supreme Court's confirmation in *Albrecht* that preemption is a legal question for judges to decide, the basis for preemption is even stronger today than it was when this Court first granted defendants' motion for summary judgment. Adding a pancreatic cancer warning to the labeling of incretin-based therapies would "irreconcilably conflict," *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1679 (2019), with the FDA's considered conclusion that "a warning or other reference to [pancreatic cancer] is unsubstantiated," *In re Incretin-Based Therapies Prods. Liab. Litig.*, 142 F. Supp. 3d 1108, 1132 (S.D. Cal. 2015).

Plaintiffs' arguments in response are recycled: (1) preemption is available only where the FDA has rejected a manufacturer's request for a labeling change; (2) the FDA's conclusions about the pancreatic safety of incretin-based therapies do not reflect the Agency's "official position," are preliminary, and were not reached pursuant to congressionally delegated authority; and (3) the FDA was not aware of purported "material safety information" that might have altered the Agency's conclusions about the pancreatic safety of one or more of the products at issue in this litigation. These arguments are as bootless now as they were in 2015.

First, this Court correctly found that the FDA's evaluation of the pancreatic safety of incretin-based therapies was "more thorough than a review of relevant data offered in connection with a CBE and PAS," and the "FDA's conclusions should not be subject to reevaluation simply because they were not articulated in connection with a CBE or PAS rejection." *Id.* at 1125–26. That is consistent with *Albrecht*, which makes clear that there are multiple ways by which the Agency can express its disapproval of a warning, and "make[s] only the obvious point that, ***whatever the means the FDA uses*** to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated." 139 S. Ct. at 1679 (emphasis added).

Second, this Court correctly found that the Agency's actions were "squarely within the FDA's congressionally delegated authority to regulate the safety of prescription drugs" and that "the Assessment and citizen petition response constitute the FDA's official position regarding pancreatic safety." 142 F. Supp. 3d at 1126–27. Nothing in *Albrecht* changes that conclusion.

Third, this Court's task is to determine for each manufacturer whether "newly acquired information" exists as to its product that would have warranted that defendant's submission of a CBE. *Albrecht* confirms that, as a threshold matter, "manufacturers cannot propose a change that is not based on reasonable evidence." 139 S. Ct. at 1679. Whether there is "newly acquired information" under 21 C.F.R. § 314.70, the regulation setting forth the requirements for a CBE, is a threshold question. If the purported "new safety information" plaintiffs identify does not qualify as "newly acquired information," preemption applies independent of the Court's "clear evidence" analysis. *See Albrecht*, 139 S. Ct. at 1679; *Wyeth v. Levine*, 555 U.S. 555, 568 (2009). The purportedly "new" information is not new to the FDA; plaintiffs do not offer expert or other evidence that it would be scientifically material to the FDA's decision making; and plaintiffs' own general causation experts do not suggest it reflects "reasonable evidence of a causal association," the regulatory threshold for adding a warning to FDA-approved labeling. 21 C.F.R. § 201.57(c)(6)(i).

In short, this Court should grant summary judgment based on preemption for two reasons—first, because adding a pancreatic cancer warning to the labeling of incretin-based therapies would "irreconcilably conflict" with the FDA's conclusion that such a warning is not substantiated by available scientific information; and second, because there was not "newly acquired information" justifying a label change application in the first place.

ARGUMENT

I. Preemption Is Not Limited to Instances Where the FDA Has Rejected a CBE or PAS.

This Court previously considered and "reject[ed] Plaintiffs' position that Defendants cannot establish preemption absent express rejection of a proposed labeling change." 142 F. Supp. 3d at 1124; *see also id.* at 1125 ("the FDA's review of pancreatic safety was ***more thorough*** than a review of relevant data offered in connection with a CBE or PAS"[1]). Plaintiffs renew that argument, claiming that *Albrecht* "placed new limitations on how a drug company can establish preemption," namely by limiting its application to instances where a drug manufacturer has requested a labeling change.[2]

That is incorrect. *Albrecht* did not place "new limitations" on the methods by which preemption can apply, but expressly noted that "[t]he question of [the FDA's] disapproval 'method' is not now before us." 139 S. Ct. at 1679; *see also Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882, 891 (7th Cir. 2020) ("*Albrecht* provided important guidance but did not break new ground"). It is not surprising, of course, that *Albrecht* includes rejection of a manufacturer-proposed labeling change as one disapproval method—that is, after all, specifically what the underlying facts in that case involved, 139 S. Ct. at 1675—but the Supreme Court also acknowledged that there is more than one method by which the Agency can disapprove of a warning, so long as "***whatever the means*** the FDA uses to exercise its authority, those means … lie within the scope of the authority Congress has lawfully delegated." *Id.* at 1679. In fact, only a few pages after contending that preemption is unavailable without a manufacturer-proposed labeling change, Opp'n at 13, plaintiffs concede that the

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[1] All emphases are added unless otherwise indicated.

[2] Plaintiffs' Opposition to Defendants' Motion for Summary Judgment on the Affirmative Defense of Preemption ("Opp'n") at 13.

Supreme Court specifically identified other agency actions that "can establish preemption," *id.* at 19 (citing *Albrecht*, 139 S. Ct. at 1679). In other words, as plaintiffs correctly point out, a "[f]ormal rejection of [a] warning label" is only one of several bases for preemption identified by the Court. *Id.*

Plaintiffs' opposition also fails to acknowledge, much less respond to, cases decided after *Albrecht* recognizing that preemption can apply in contexts other than the submission and rejection of a CBE or PAS. *See, e.g.*, *Cerveny v. Aventis, Inc.*, 783 F. App'x 804, 808 n.9 (10th Cir. 2019) (defendant need not demonstrate that the FDA "would have rejected any unilateral label change under the CBE regulation" where it had a "separate avenue" in the FDA's unequivocal rejection of a citizen's petition "advocating for the warning that the [plaintiffs] now assert"); *Ridings v. Maurice*, 444 F. Supp. 3d 973, 998 (W.D. Mo. 2020) ("FDA's continued inaction" "in light of the known issues and the ongoing give-and-take between [defendant] and the FDA on these issues … represent[ed] clear evidence under these facts"); *Thomas v. Bracco Diagnostics*, 2020 WL 1016273, at *10 (W.D. La. Feb. 27, 2020) (finding "clear evidence that FDA would not have approved a warning" based on the Agency's conclusions that scientific data did not justify a "causal relationship"); *Smith v. GE Healthcare Inc.*, 2020 WL 1880787, at *7 (W.D. La. Mar. 31, 2020).

The concurring opinion in *Albrecht* correctly points out that the FDA's duty to regulate safety information in drug labeling under 21 U.S.C. § 355(*o*)(4)(A) "does not depend on whether the relevant drug manufacturer, as opposed to some other entity or individual, brought the new information to the FDA's attention."[3] 139 S. Ct. at 1684 (Alito, J., concurring); *see also, e.g.*, *Cerveny*, 783 F. App'x at 808 n.9 (finding preemption based on FDA rejection of a citizen petition); *Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1274, 1277 (W.D. Okla. 2011) (finding preemption based in part on

[3] § 355(*o*)(4)(A) requires, inter alia, FDA to notify the drug manufacturer of new safety information FDA becomes aware of and determines should be added to a drug's labeling.

rejection of multiple citizen petitions). Plaintiffs say this carries "no weight whatsoever." Opp'n at 13. That, too, is incorrect. The concurring opinion is persuasive authority consistent with the majority. *See, e.g.*, *United States v. Garcia*, 877 F.3d 944, 950 n.4 (10th Cir. 2017) ("Although a concurring opinion is not binding on us, we may consider it for its persuasive value."); *Mont. Envtl. Info. Ctr. v. Stone-Manning*, 766 F.3d 1184, 1190–91 (9th Cir. 2014) (adopting and expanding on a rule originating in Justice O'Connor's concurrence in *Reno v. Catholic Social Services*, 509 U.S. 43, 67 (1993)). And plaintiffs concede that, in keeping with the concurrence, *Albrecht* listed FDA action pursuant to § 355(*o*)(4)(A) as one of the "[o]ther agency actions carrying the force of law" that "can establish preemption." Opp'n at 19 (citing *Albrecht*, 139 S. Ct. at 1679).

As this Court held in 2015, because the FDA conducted an evaluation that was "more thorough than a review of relevant data offered in connection with a CBE and PAS," the Agency's "conclusions should not be subject to reevaluation simply because they were not articulated in connection with a CBE or PAS rejection." 142 F. Supp. 3d at 1125–26. Plaintiffs' own regulatory expert, Dr. Alexander Fleming, acknowledged that the FDA's evaluation was "unprecedented," that it "reflect[ed] a very robust evaluation that went on for a significant period of time," and that "[i]t would be a little absurd" for the FDA to endorse a pancreatic cancer warning that its "comprehensive evaluation" found was inconsistent with available scientific data.[4]

II. FDA's Actions Are Squarely Within Its Congressionally Delegated Authority.

Plaintiffs recycle another previously-rejected argument—that the FDA's Assessment and rejection of the citizen's petition do not constitute official or final Agency action taken pursuant to congressionally delegated authority. In 2015, the

[4] G. Alexander Fleming, M.D. Deposition Tr. (May 22, 2015) at 92:13–16, 201:21–202:1 (Ex. B to Apr. 22, 2020 Declaration of Paul E. Boehm in Supp. of Defs.' Mot. for Summ. J., Doc. No. 3522-2 (hereinafter "Ex."))

Court found that "[t]he FDA's review of pancreatic safety data of the drugs at issue ***falls squarely within the FDA's congressionally delegated authority*** to regulate the safety of prescription drugs." 142 F. Supp. 3d at 1126–27. Plaintiffs contend that *Albrecht* requires a different conclusion. It does not. *Albrecht* merely confirms that courts must consider whether the Agency's actions were made pursuant to congressionally delegated authority, which this Court did.

A. FDA Acted Within Its Congressionally Delegated Authority.

Albrecht "make[s] only the obvious point that, whatever the means the FDA uses to exercise its authority, those means must lie within the scope of the authority Congress has lawfully delegated." 139 S. Ct. at 1679. This Court considered that very question in 2015, finding that the FDA acted "squarely within [its] congressionally delegated authority." 142 F. Supp. 3d at 1126.[5]

While *Albrecht* recognizes that the FDA may use a variety of means to express its disapproval of a proposed warning, plaintiffs contend only three exist. Opp'n at 19. Even that cramped listing, however, betrays the flexibility available to the FDA, for plaintiffs' third "means" of action is "[o]ther agency actions carrying the force of law." *Id.* *Albrecht* does not provide an exhaustive listing of means "within the scope of the authority Congress has lawfully delegated" because the issue of specific "disapproval 'method' [was] not before [the Court]." 139 S. Ct. at 1679.[6]

None of the other cases plaintiffs cite advance their argument, either. Plaintiffs badly mischaracterize the Third Circuit's decision in *In re Avandia Marketing*, 945 F.3d 749 (3d Cir. 2019). There, the court held that the manufacturer could not show that the FDA, in rejecting the manufacturer's PAS, was "fully informed" because it was not actually communicating disapproval of a labeling change; rather, the FDA

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[5] In doing so, the Court relied on *Reid v. Johnson & Johnson*, 780 F.3d 952, 964 (9th Cir. 2015), so it is strange that plaintiffs urge the Court to consider *Reid* as if it had not already done so, *see* Opp'n at 18.

[6] Each example of FDA action to which the opinion refers is accompanied by "*e.g.*"

told the manufacturer that "the information [it] presented is inadequate" and subsequently "*ordered* [it] to include various warnings" about the injury at issue. *Id.* at 758, 760 (emphasis in original). The contrasts are obvious—here, the FDA "conducted an independent review of pancreatic safety and concluded scientific evidence did not support any changes to the product labeling." 142 F. Supp. 3d at 1125. In addition, since 2015, the FDA has approved four new incretin-based therapies, as well as more than 50 additional labeling changes for the specific medicines at issue in this litigation. In each case, the FDA approved the labeling without mandating a pancreatic cancer warning.[7] "While FDA inaction is insufficient on its own to establish preemption, it is highly persuasive given the FDA's comprehensive review of pancreatic safety and ability to mandate a labeling change if it concluded the regulatory standards were satisfied." 142 F. Supp. 3d at 1123; *see also Ridings*, 444 F. Supp. 3d at 998 (finding that "FDA's continued inaction" "in light of the known issues and the ongoing give-and-take between [defendant] and the FDA on these issues … represent[ed] clear evidence under these facts").[8]

Plaintiffs similarly mischaracterize *Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882 (7th Cir. 2020), claiming that it "found that *Albrecht* appeared to have abolished impossibility preemption based on what the FDA 'would have' done." Opp'n at 21.

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[7] Defs.' Mem. in Supp. of Defs.' Mot. for Summ. J. Based on Preemption ("Opening Br.") at 10–12.

[8] Plaintiffs contend that by declining to address the effect of the FDAAA amendments of 2007, the *Albrecht* majority "rejected" the idea that FDA inaction informs the "clear evidence" analysis. Opp'n at 13–14. The Supreme Court did no such thing. In *Albrecht*, given the duties imposed by the 2007 amendments, Merck argued that the FDA's inaction was relevant evidence of its intentions. The majority did not take up that issue, expressly declining to address "[t]he question of disapproval 'method.'" 139 S. Ct. at 1679. Justice Alito observed, without contradiction, that the majority's decision therefore did not preclude the Third Circuit from considering on remand "the effect of [21 U.S.C.] § 355(*o*)(4)(A) on the pre-emption issue in this case." *Id.* at 1684–85 (Alito, J., concurring).

The quoted paragraphs, however, are part of the Seventh Circuit's recitation of the plaintiffs' position on appeal, not the court's reasoning or holding. 951 F.3d at 890. The Seventh Circuit affirmed the district court's decision dismissing the matter based on preemption, observing that "*Albrecht* brought the *Wyeth* 'clear evidence' holding into sharper focus. It did not adopt a new rule of preemption law." *Id*. at 891.

In other words, there are no new facts or law to change this Court's determination that the Agency's actions here are "squarely within its congressionally delegated authority."[9]

B. FDA's Conclusions About the Pancreatic Safety of Incretin-Based Therapies Reflect the Views of the Agency.

Plaintiffs claim that the FDA's conclusions on the pancreatic safety of incretin-based therapies—no matter how robust its evaluation, or how clear its findings—do not reflect the Agency's official position. But again, the Court considered this question and reached the opposite conclusion: "the Court finds the Assessment and citizen petition response constitute the FDA's official position regarding pancreatic safety, as both fall within the FDA's congressionally delegated regulatory authority." 142 F. Supp. 3d at 1126–27; *see also Seufert v. Merck Sharp & Dohme Corp.*, 187 F. Supp. 3d 1163, 1173–74 & n.15 (S.D. Cal. 2016) (holding that the 2014 Assessment represented "the FDA's conclusions"). Plaintiffs refer to 21 C.F.R. § 10.85(k) for the proposition that the FDA Assessment "expressly does not represent the FDA's position." Opp'n at 20. This is incorrect. Although § 10.85(k) cautions that a written statement by FDA employees "does not ***necessarily*** represent the formal

[9] Plaintiffs also cite two district court opinions, but each held only that preemption was "premature" at the motion to dismiss stage. In one, defendants cited only "a single paragraph in the Complaint." *Crockett v. Luitpold Pharm., Inc.*, No. 19-276, 2020 WL 433367, at *7 (E.D. Pa. Jan. 28, 2020). In the other, the defendant did not "point to any evidence … that the FDA would have rejected a different warning label." *Atkinson v. Luitpold Pharm., Inc.*, No. 19-277, 2020 WL 1330705, at *3 (E.D. Pa. Mar. 23, 2020).

position of FDA," the 2014 Assessment "is written from the FDA's perspective and lacks the disclaimer required when publications of FDA employees do not necessarily reflect the opinions of the agency." 142 F. Supp. 3d at 1126. The Assessment states that "***the FDA*** and the EMA … agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data," and that "***[t]he FDA*** and the EMA believe that the current knowledge is adequately reflected in the product information or labeling."[10] Even plaintiffs' expert, Dr. Fleming, acknowledged that the Assessment "represents FDA's position."[11]

Plaintiffs also contend that the FDA's Assessment does not reflect its final conclusion on the matter. Opp'n at 22. This, too, rehashes an argument this Court rejected five years ago: "the FDA's ongoing review of pancreatic safety [is] more indicative of the evolving nature of drug surveillance, than of the existence of a causal association." 142 F. Supp. 3d at 1128. As the Court previously explained, the FDA is continually reviewing safety data for drugs on the market,[12] and as such no FDA determination about drug safety can be final for all time. "The potential for the FDA to reach a different conclusion in the future in light of new scientific evidence or developments does not preclude a finding of preemption now." 142 F. Supp. 3d at 1128.[13] Here, the Agency's pledge to "continue to investigate" the pancreatic safety

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[10] FDA Assessment (Ex. A) at 796.

[11] Fleming Tr. (Ex. B) at 84:22–25.

[12] *See, e.g.*, 21 U.S.C. § 355(*o*)(4) (requiring the FDA to act on "new safety information" that may affect "the labeling of the drug").

[13] Plaintiffs cite *In re Testosterone Replacement Therapy*, 430 F. Supp. 3d 516 (N.D. Ill. 2019), for the proposition that an FDA statement that studies and trials are "inconclusive for determining risk," precludes a finding of preemption. Opp'n at 22. *In re Testosterone* is inapposite in that the court relied heavily on the fact that the FDA ultimately "recognized that there *is* evidence of an association." 430 F. Supp. 3d at 530 (emphasis in original).

of incretin-based therapies in the context of its comprehensive Assessment only undermines plaintiffs' opposition—in the years since its Assessment, the FDA has continued to consider and approve numerous labeling changes, expand treatment indications, and approve additional incretin-based therapies, all without requiring a warning for pancreatic cancer.

III. Plaintiffs' Purported Safety Information Is Not "Newly Acquired Information," And FDA's Conclusions Are Fully Informed.

With respect to plaintiffs' purported "material safety information," there are three distinct questions of law for the Court to decide:

1. *Does plaintiffs' purported "material safety information" constitute "newly acquired information" such that defendants could submit a CBE labeling change?* As *Albrecht* notes, "manufacturers cannot propose a change that is not based on reasonable evidence. [21 C.F.R.] § 314.70(c)(6)(iii)(A)." 139 S. Ct. at 1679.[14] This means that "[p]ost-FDA approval preemption analysis proceeds in two stages. First the plaintiff must show that there existed 'newly acquired information' such that the defendants could unilaterally change the label pursuant to the CBE regulation without FDA approval." *Utts v. Bristol-Myers Squibb Co.*, 251 F. Supp. 3d 644, 661 (E.D.N.Y. 2017), *aff'd sub nom. Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699 (2d Cir. 2019); *see also McGrath v. Bayer Healthcare Pharm., Inc.*, 393 F. Supp. 3d 161, 166–68 (E.D.N.Y. 2019); *Goodell v. Bayer Healthcare Pharm. Inc.*, 2019 WL 4771136, at *4 (D. Mass. Sept. 30, 2019). In other words, "if there is no newly

[14] *See also McGrath*, 393 F. Supp. 3d at 167 ("[N]ewly acquired information 'must provide *reasonable evidence* of a causal association of a clinically significant adverse reaction linked to a drug.'") (quoting 21 C.F.R. § 201.57(c)(6)(i)) (emphasis in original); 142 F. Supp. 3d at 1112 ("[A]n indeterminate causal association falls below the federal regulatory standards required for labeling changes."). The information also "must have revealed risks of a different type or greater severity or frequency than previously included in submissions to the FDA." *Gibbons*, 919 F.3d at 708 (internal quotations omitted).

acquired information, then the manufacturer is under no duty to change its label and related state failure to warn claims are preempted." *Roberto v. Boehringer Ingelheim Pharm.*, 2019 WL 5068452, at *11 (Conn. Super. Ct. Sept. 11, 2019) (c*iting Utts*, 251 F. Supp. 3d at 673).[15] This basis for preemption is independent of the "clear evidence" test set forth in *Wyeth* and *Albrecht*.

Here, there is no relevant "newly acquired information" that, under federal law, would qualify for a CBE adding the pancreatic cancer warning plaintiffs contend is required by state law. This is particularly clear given the FDA's Assessment, which involved review of an "unprecedented" volume of information from a wide-ranging array of sources. Because plaintiffs' purported "material safety information" does not amount to "newly acquired information"—an issue that plaintiffs' opposition elides—plaintiffs' claims are preempted.

2. *Was the FDA "fully informed" of material safety information in concluding that a causal association between incretin-based therapies and pancreatic cancer is not substantiated by available scientific data and that the current labeling is adequate?* "[T]he mere availability of a CBE label amendment does not necessarily defeat a manufacturer's preemption defense. Because the FDA 'retains the authority to reject labeling changes,' a manufacturer may still—even after the plaintiff has identified 'newly acquired information'—establish an impossibility preemption defense through 'clear evidence that the FDA would not have approved a change' to the label." *Utts*, 251 F. Supp. 3d at 661 (quoting *Wyeth*, 555 U.S. at 571). The "clear evidence" test requires that the Agency be "fully informed" of the reasonable justifications for the warning plaintiffs advocate. *Albrecht*, 139 S. Ct. at 1678. Here, the FDA was fully informed of all material information allegedly supporting a

[15] *See also, e.g.*, *Ridings*, 444 F. Supp. 3d at 990–91; *Mahnke v. Bayer Corp.*, 2020 WL 2048622, at *5 (C.D. Cal. Mar. 10, 2020); *Adkins v Boehringer Ingelheim Pharm., Inc.*, 2020 WL 1704646 at *3–4 (Conn. Super. Ct. Mar. 13, 2020).

pancreatic cancer warning.[16] That is particularly clear given the close attention paid by the Agency to this issue over the course of many years. It is also clear based on a careful look at the purported "material safety information," as explained below.

3. *Is it the "law of the case" that defendants failed to submit all material safety information to the FDA?* Plaintiffs' contention that the "law of the case" precludes summary judgment misreads this Court's 2015 decision and the Ninth Circuit's finding on appeal. In opposing the 2015 motions, plaintiffs argued that certain data that defendants allegedly withheld from the FDA "constitute[d] new safety information within the meaning of federal labeling regulations." 142 F. Supp. 3d at 1129. The Court held that plaintiffs' allegations amounted to "fraud-on-the-FDA claims" that were preempted under *Buckman v. Plaintiffs' Legal Committee*, 531 U.S. 341 (2001), and therefore it could not consider the information as part of its "clear evidence" analysis. 142 F. Supp. 3d at 1129–30. The Court noted that, in any event, "it remains unclear whether the FDA considered this information, and if it did not, whether this data would have altered the FDA's conclusion," given that "[t]he parties' experts dispute whether the information was material to the FDA's analysis and offer little clarity on this point." *Id.* at 1130.

On appeal, the Ninth Circuit held that *Buckman* did not "preclude discovery of evidence relevant to the plaintiffs' state-law failure-to-warn claims," and that this Court erred by "deem[ing] the new safety information irrelevant at the summary judgment stage." *In re Incretin-Based Therapies Prods. Liab. Litig.*, 721 F. App'x

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[16] Plaintiffs cite *Risperdal & Invega Cases*, 263 Cal. Rptr. 3d 412 (2020), for the proposition that scientific information cumulative of what the FDA already has can nevertheless constitute "newly acquired information." Opp'n at 16. This mischaracterizes the ruling. There, the table of data at issue could "support a potential label change via the CBE regulation" precisely because the table "provided additional information" on the adverse effects of the drug in question relative to "the studies submitted to the FDA." 264 Cal. Rptr. 3d at 425. As discussed below, the data plaintiffs identify here provides no such "additional information." *Id.*

580, 583–84 (9th Cir. 2017). Relying on this Court's observation that in light of conflicting expert testimony it "remains unclear" whether the FDA considered the new information or whether that information would have been material, the Ninth Circuit explained that the Court's uncertainty "should have prevented entry of summary judgment." *Id.* at 584. But instead of reversing this Court's summary judgment finding—which it would have done had it found the information was material as a matter of law, *see, e.g.*, *Messick v. Novartis Pharm. Corp.*, 747 F.3d 1193, 1199 (9th Cir. 2014)—the Ninth Circuit vacated and remanded the case to this Court. 721 F. App'x at 584.

Plaintiffs' argument also is at odds with their withdrawal of the expert testimony that gave this Court pause in 2015. In particular, plaintiffs have now withdrawn the portions of Dr. Fleming's report relating to the materiality of the purported "safety information." *See* Opening Br. at 21 n.66. As a result, the only evidence on materiality is that of defendants' expert, Dr. Goldkind, who testified that the data plaintiffs identify "is ***cumulative and repetitive*** of the very safety information the FDA already has considered." *Id.* at 21; *see also Gibbons*, 919 F.3d at 708 (holding that "newly acquired information" must reveal "risks of a different type or greater severity or frequency than previously included in submissions to the FDA" (quoting 21 C.F.R. § 314.3)). In other words, there is no longer any dispute among the experts over "whether the information was material to the FDA's analysis." 142 F. Supp. 3d at 1130; 721 F. App'x at 584 ("[T]he parties' experts disputed whether the 'new safety information' would have been material to the FDA's analysis.").

A. Sitagliptin (Januvia and Janumet)

Plaintiffs contend that the FDA might not be "fully informed" of certain "material safety information," thereby precluding preemption for Merck under the "clear evidence" test. They do not address the threshold question of whether the purported "safety information" they identify amounts to "newly acquired information" under the CBE regulation, § 314.70. Putting that problem aside, plaintiffs point to

(i) a preliminary signal assessment performed by Health Canada in November 2013; (ii) a purported "clinical trial imbalance" in sitagliptin clinical trials; (iii) a 2014 amendment to the clinical study protocol for TECOS requiring the collection of specified events more than 28 days after a patient had discontinued from the study; and (iv) nonclinical studies involving desfluorositagliptin, an experimental compound that no plaintiff in this litigation (or any human being ever) has used.

Health Canada Preliminary Signal Assessment. Plaintiffs say in passing that it is not clear whether "the FDA reviewed it prior to the 2014 NEJM article." Opp'n at 26. For all of the reasons set forth in the opening brief—none of which plaintiffs respond to—the preliminary assessment performed by Health Canada is not material and does not constitute "newly acquired information" under § 314.70. It involves application of regulatory standards that do not apply to the FDA; does not address any stream of data the FDA has not itself carefully considered; did not reveal new risk information; did not conclude that there was "reasonable evidence of a causal association"; and was not final—as plaintiffs know, it was updated in 2016 to confirm Health Canada's view that "***existing data do not suggest a causal relationship*** between incretin-based therapies and the development of [pancreatic cancer]." Opening Br. at 23–25. The preliminary assessment performed by Health Canada is neither material, nor does it amount to "newly acquired information."

"Clinical Trial Imbalance." Plaintiffs cite no evidence for their continued claim that sitagliptin clinical trials reveal an overall numerical imbalance of 6 to 3. Even if it were the case—which it is not—plaintiffs fail to identify, nor have their experts performed, any statistical analysis based on these purported numbers. Statistical associations, not purported "numerical imbalances," take into account the

number of patient-years of observation in each arm of the analysis to compare the incidence rates of disease in an exposed group and a control group.[17]

The so-called "misrepresentation" to which plaintiffs refer is rooted in a 2013 peer-reviewed pooled analysis—published in a publicly-available medical journal and available to the FDA—of ***a specifically-designed subset*** of sitagliptin clinical studies in patients (i) treated with a 100mg/day dose (ii) for between 12 weeks and 2 years (iii) that were completed as of December 2011.[18] The study authors expressly defined these criteria in the publication itself:

> METHODS
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> This post hoc analysis used a pooled population ($n = 14,611$) drawn from all 25 multicenter, US or multinational, double-blind, parallel-group studies conducted by Merck & Co., Inc., in which patients were randomized to receive sitagliptin 100 mg/day ($n = 7,726$) or a comparator ($n = 6,885$) for at least 12 weeks and up to 2 years (the duration of the longest studies) and for which results were available as of December 1, 2011 (complete study listing in Table 6 in Appendix).

Engel Analysis (Ex. AV to Boehm Supp. Decl.) at 3. This is the publication to which plaintiffs refer in their opposition. This publication is repeatedly and specifically referenced throughout the Development Safety Update Report ("DSUR") that plaintiffs claim was misleading.[19] Contrary to plaintiffs' suggestion that Merck

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[17] *See* Fed. Judicial Ctr., *Reference Manual on Scientific Evidence* 566–67 (3d ed. 2011) (Ex. AK).

[18] Samuel S. Engel, et al., *Safety and Tolerability of Sitagliptin in Type 2 Diabetes: Pooled Analysis of 25 Clinical Studies*, Diabetes Therapy 2013; 8:119–45 ("Engel Analysis") (attached as Ex. AV to the Supplemental Declaration of Paul E. Boehm (hereinafter "Boehm Supp. Decl.")).

[19] MRKJAN0003289815 at 43–45, 82, 163, 198, 204, 250, 331, 366, 368, 408 (relevant portions attached as Ex. AW to Boehm Supp. Decl.).

"misrepresent[ed] its clinical trial data," Opp'n at 40, Merck explicitly informed the FDA that the pooled analysis did not include certain studies, and Merck explained in detail why those studies were excluded.[20]

Plaintiffs do not dispute that they have retained two expert biostatisticians in this litigation, one of whom, Dr. David Madigan, performed a statistical analysis of all available sitagliptin clinical trial data available ***as of 2015***. Dr. Madigan's analysis—like every meta-analysis published in the peer-reviewed literature and performed by other experts in this litigation—does not reveal an association between sitagliptin and pancreatic cancer.[21] In sum, a purported overall "numerical imbalance" in the sitagliptin clinical trial data is the creation of plaintiffs' counsel, is nowhere to be found in the evidence, and is rebutted by the statistical analysis of plaintiffs' own expert. It cannot be material to FDA's conclusions, nor can it constitute "newly acquired information" under § 314.70.

TECOS Protocol Amendment. Next, plaintiffs contend that the FDA is not "fully informed" about the inclusion of three pancreatic cancer events in the TECOS study that occurred more than 28 days after those individuals discontinued use of the treatment to which they were assigned (in this case, placebo), but before the TECOS study protocol was amended in 2014 to require collection of certain events that occurred more than 28 days after discontinuation.[22] This is impossible. The very documents plaintiffs cite about the TECOS study protocol, the 2014 protocol

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[20] MRKJAN0003289815 (Ex. AW to Boehm Supp. Decl.) at 169, 336; MRKJAN0003241484 at 111 (relevant portions attached as Ex. BV to Boehm Supp. Decl.).

[21] Merck's Mem. in Support of Mot. for Summ. J. (Doc. No. 3524-1) at 4–10.

[22] Even before the 2014 protocol amendment, the original TECOS protocol provided that "[t]he clinical events list and [serious adverse events] Modules will be reviewed and completed *each time the patient is seen in follow up*"—regardless of how long it had been since study drug discontinuation. MRKJAN0004004352 (relevant portions attached as Ex. AX to Boehm Supp. Decl.) at 35.

amendment, and the specific information about each of these three individuals are among the files constituting Merck's communications ***with the FDA***.[23]

Plaintiffs seemingly seek to imply that scientific researchers from Oxford and Duke Universities who conducted the TECOS study may have altered the pancreatic cancer results by more assiduously counting events in the placebo arm than events in the sitagliptin arm. This ignores that the physicians responsible both for reporting events and the specialists responsible for adjudicating them were blinded as to which arm of the study individual patients were enrolled in.[24] They could hardly have recorded events differently for sitagliptin and placebo patients if they did not know which patients were in which arm of the study, and plaintiffs present no evidence otherwise. In any event, even if one were to exclude the "adjudicated-yes placebo cases" that plaintiffs contend skew the TECOS numbers, Opp'n at 42 (emphasis omitted)—and to be clear, there is no basis for doing that—there still would be more pancreatic cancer events in the placebo arm (11) than in the sitagliptin arm (9).[25]

Plaintiffs raise other questions about TECOS, all of which easily could have been answered if they had proceeded with the deposition of Dr. Samuel Engel, the researcher at Merck Research Labs most knowledgeable about TECOS. Instead, plaintiffs elected to cancel Dr. Engel's deposition less than two days before it was scheduled to proceed. Regardless, all of the purported issues plaintiffs identify were contained in Merck's communications ***with the FDA***.[26] Indeed, although plaintiffs mischaracterize the underlying facts, they correctly point out that the FDA has paid

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[23] *E.g.*, MRKJAN-CC0000493967 (Ex. AY to Boehm Supp. Decl.) (cover letter to FDA discussing TECOS protocol amendment).

[24] MRKJAN0004004352 (Ex. AX to Boehm Supp. Decl.) at 12, 22–23.

[25] MRKJAN0005019776 (Ex. 43 to the Declaration of Tor A. Hoerman in Support of Plaintiffs' Opposition, Doc. No. 3721-1 (hereinafter "Opp'n Ex.")).

[26] *E.g.*, MRKJAN-CC0000493967 (Ex. AY to Boehm Supp. Decl.) (cover letter to FDA discussing TECOS protocol amendment).

close attention to results from TECOS. Meanwhile, no expert in this litigation has called into question the pancreatic cancer results from the TECOS study; plaintiffs' own expert biostatistician, Dr. David Madigan, testified that it is "scientifically appropriate" to include TECOS data in any meta-analysis of sitagliptin clinical trial data; and the peer-reviewed publication of the study's final results remain publicly available.[27]

No amount of massaging data from the TECOS study can render the information plaintiffs identify material to the Agency's conclusions about sitagliptin's pancreatic safety or "newly acquired information" under § 314.70.

Desfluorositagliptin. Finally, plaintiffs cast various aspersions on Merck's development and use of desfluorositagliptin, a compound that is not at issue in this litigation. Desfluorositagliptin is not sitagliptin. As background, desfluorositagliptin is a DPP-4 inhibiting compound that shares certain properties with sitagliptin—it is, as plaintiffs point out, "virtually identical" in terms of potency, selectivity, and pharmacokinetics. But this is not a complete listing of all pharmaceutical characteristics, and desfluorositagliptin has "many other features associated with the molecule that are not the same" and these "are by nature two different molecules."[28]

Desfluorositagliptin has not been developed for clinical use. It is not on the market as a prescription medicine. No plaintiff in this litigation has taken desfluorositagliptin and alleged that it caused an injury. Indeed, no human has ever

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[27] David Madigan, Ph.D. Deposition Tr. (Oct. 19, 2015) at 154:19–155:15 (relevant portions attached as Ex. AZ to Boehm Supp. Decl.); *see also* Merck's Reply in Support of Mot. for Summ. J. at 7–8. The peer-reviewed publication is available at https://www.nejm.org/doi/full/10.1056/nejmoa1501352 (last visited Sept. 1, 2020).

[28] Bei Zhang, Ph.D. Deposition Tr. (July 24, 2019) at 147:17–148:12 (relevant portions attached as Ex. BA to Boehm Supp. Decl.); *see also* Nancy Thornberry Deposition Tr. (Sept. 29, 2016) at 99:18–23 (relevant portions attached as Ex. BB to Boehm Supp. Decl.) (testifying that desfluorositagliptin "is not identical to sitagliptin").

ingested this compound for any purpose, not in exploratory studies, efficacy studies, or safety studies.[29] The only experiments in which desfluorositagliptin has been used are in non-clinical experimental settings (i.e., animal and petri dish experiments).

Plaintiffs' argument seemingly is that Merck nevertheless should have provided certain study results for desfluorositagliptin "to provide the FDA with more of the exact kind of data the FDA sought." Opp'n at 39. Plaintiffs point to only one specific study—a 2008 study in mice performed by a group of independent academic researchers at the University of Toronto, the results of which "had been accepted for publication" in a publicly-available, peer-reviewed scientific journal. *Id.* at 37. Plaintiffs claim "[t]his was a study that undoubtedly could have provided material safety information, but Merck did not obtain or review the samples to respond to the FDA, nor suggest that FDA review them." *Id.* at 38.

This is a curious line of attack, to be sure. Whatever the similarities or dissimilarities between desfluorositagliptin and sitagliptin, the 2008 mouse study—the only "undisclosed" desfluorositagliptin information plaintiffs specifically identify—was published and is available to anyone with an Internet connection.[30] Regardless, the study does not reveal any safety concerns related to the pancreas or otherwise.[31]

Indeed, plaintiffs do not cite any adverse safety data of any kind from studies performed using desfluorositagliptin. Bei Zhang, a former research scientist at Merck involved in desfluorositagliptin studies, testified that she could not identify a single

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[29] Zhang Tr. (Ex. BA to Boehm Supp. Decl.) at 47:4–48:20 (explaining that, although Merck used desfluorositagliptin to "conduct basic research" with "exploratory models," "the compound developed for human use is sitagliptin").

[30] Benjamin J. Lamont & Daniel J. Drucker, *Differential Antidiabetic Efficacy of Incretin Agonists Versus DPP-4 Inhibition in High Fat-Fed Mice*, Diabetes 57:1 at 190–198 (Jan. 2008), *available at* https://pubmed.ncbi.nlm.nih.gov/17928394/ (attached as Ex. BC to Boehm Supp. Decl.).

[31] *See id.* (Ex. BC to Boehm Supp. Decl.) at 191–93.

desfluorositagliptin study conducted by Merck that resulted in negative safety information related to the pancreas—this included basic research studies, safety assessment studies, and exploratory experiments.[32] Of the more than 120 desfluorositagliptin studies available through a basic PubMed search, plaintiffs cannot identify a single one that raises concerns about pancreatic toxicity. Of the more than 200 references to desfluorositagliptin studies in Merck's communication files with the FDA, plaintiffs cannot identify a single one that raises concerns about pancreatic toxicity. Of the more than 40 published, unpublished, and internal studies that Merck has identified, summarized, and produced to plaintiffs over the course of this litigation—as part of its 37 million pages and 2,700 gigabytes of raw data of productions—plaintiffs cannot identify a single one that raises concerns about pancreatic toxicity. In short, although plaintiffs claim that desfluorositagliptin studies were "done for the purpose of concealing from the FDA information that Merck obtained about sitagliptin by testing desfluorositagliptin," Opp'n at 39, they fail to identify any adverse safety information from the hundreds of desfluorositagliptin studies available to them. In fact, plaintiffs complain that Merck knew in advance that sitagliptin studies "***would be favorable*** because it had first researched the issue with desfluorositagliptin." *Id.*[33]

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[32] Zhang Tr. (Ex. BA to Boehm Supp. Decl.) at 421:10–21, 437:7–438:11. Dr. Zhang further testified that pharmaceutical companies commonly use analog compounds, including to better structure studies that will later be used with the compound-in-development. *Id*. (Ex. BA to Boehm Supp. Decl.) at 36:9–38:7.

[33] Also without substance is the claim that "Merck proceeded to hide [desfluorositagliptin data] from Plaintiffs … , despite being under a court order to produce it." Opp'n at 39. The facts are that after hearing a discovery motion on this issue in November 2018, the Court told plaintiffs to raise the issue again if they were unsatisfied with Merck's document productions relating to desfluorositagliptin. Tr. of Nov. 1, 2018 Hearing (Doc. No. 2731) at 38:20–39:21. Plaintiffs never did.

Moreover, even if plaintiffs had been able to identify any data suggesting concerns about pancreatic toxicity arising from desfluorositagliptin studies *in vitro* and in animals—i.e., non-human studies in a compound not at issue in this litigation—those data would constitute, at the very most, a safety signal with respect to actual effects of sitagliptin (Januvia and Janumet) in humans. "The existence of a safety signal is not, without more, indicative of a causal association." 142 F. Supp. 3d at 1127. And, as discussed at length above, the FDA has long been aware of the pancreatic cancer safety signal and found that it does not warrant a labeling change for sitagliptin. *Id.* at 1125–27.

In sum, plaintiffs have not identified any "material safety information" related to sitagliptin—through the windy path of desfluorositagliptin, or otherwise—nor do plaintiffs show that desfluorositagliptin data could possibly constitute "newly acquired information" that "provide[s] *reasonable evidence* of a causal association" between sitagliptin and pancreatic cancer. *See McGrath*, 393 F. Supp. 3d at 167.

B. Exenatide (Byetta)

Plaintiffs claim there are three types of "material safety information" that Amylin allegedly "failed to provide" the FDA: (1) plaintiffs' own litigation expert's "re-analysis" of slide images from a non-human primate study purporting to find "PanIN" lesions; (2) Amylin's presentation of pancreatic cancer events in its clinical trials; and (3) "compromised data collection" in the EXSCEL cardiovascular outcome randomized clinical trial. Plaintiffs' arguments should be rejected as matter of law, because:

- Plaintiffs do not, and cannot, contend that any of this purported "safety information" constitutes "newly acquired information" under 21 C.F.R. § 314.70, and it therefore cannot justify a company change to the exenatide labeling.

- Plaintiffs admit that FDA already has ***all*** the underlying articles and clinical trial data they reference. Amylin did not "fail[] to provide" anything to FDA.

- Instead of producing newly acquired information, plaintiffs (without any expert support) second-guess FDA's analysis of the information that Amylin and Lilly provided. This second guessing of agency action is precisely what preemption law precludes. *See Albrecht*, 139 S. Ct. at 1672.

- No plaintiffs' expert opines that any of this so-called newly acquired information provides "reasonable evidence of a causal association," the threshold required for a warning. 21 C.F.R. § 201.57(c)(6)(i).

There is accordingly no basis to conclude that any of this information would have been "material" to the FDA and/or could have justified a labeling change.

Non-Human Primate Animal Study. According to plaintiffs, Amylin "falsely claimed to the FDA and the medical community" that there were no histopathologic changes, including PanIN lesions, in a 14-week baboon study. Opp'n at 27.[34] Plaintiffs acknowledge the FDA has this study, so by definition, it is not "newly acquired information."[35] The inquiry should end there. Instead, however, plaintiffs attempt to undermine the FDA's conclusions by relying on their litigation expert's (unreliable) reanalysis of the study slides.

The peer-reviewed, published article of the 14-week baboon study (Fiorentino 2015) evaluated pancreas tissue slides and found "no histological lesions suggestive of

[34] Plaintiffs also claim that "Amylin does not dispute" this fact. Opp'n at 27. Amylin absolutely disputes any suggestion that it "falsely claimed" anything to either FDA or the medical community. Plaintiffs do not cite any support for their assertion, which is contradicted by the evidence submitted with the pending motions. *See* Teresa V. Fiorentino, et al., *Chronic Continuous Exenatide Infusion Does Not Cause Pancreatic Inflammation and Ductal Hyperplasia in Non-Human Primates*, 185 Am. J. of Pathology 139 (Jan. 2015) ("Fiorentino Study") (Opp'n Ex. 7).

[35] This article also includes a number of images of the pancreas cells on which the authors relied in reaching their conclusions, thereby enabling FDA to reach its own conclusions.

... PanIN."[36] Plaintiffs' purported "evidence" to the contrary is an outdated expert report by Dr. Taylor prepared for this litigation. As explained in detail in defendants' accompanying motion to exclude, Dr. Taylor's purported "re-analysis" is unreliable and should be rejected.

In any event, expert testimony "unsupported by any published research" (as Dr. Taylor's is here) cannot constitute newly acquired information. *Roberto*, 2019 WL 5068452, at *19; *see also Adkins*, 2020 WL 1704646, at *9 & n.17, *11 (a "statement from a single scientist" cannot constitute newly acquired information "until that statement becomes part of a peer-reviewed article or finds other forms of corroboration"). Nor are animal data alone, such as the baboon study (much less its re-analysis, which is at issue), sufficient to trigger a label change. *Sabol v. Bayer Healthcare Pharm., Inc*., 439 F. Supp. 3d 131, 148–49 (S.D.N.Y. 2020) (animal studies that "draw only a tentative, at best, suggestion of a causal relationship" do not "draw the crucial causal link" necessary for a label change based on newly acquired evidence); *McGrath*, 393 F. Supp. 3d at 170 (animal studies not sufficient to demonstrate that a risk to humans is "apparent"). Moreover, as was explained in defendants' opening brief, plaintiffs ignore the very extensive, on-point animal toxicology analysis already performed by FDA. *See* Opening Br. at 29. As Dr. Goldkind testified: "I can't conceive of a, of an animal study that could, could change the weight of evidence of 240 studies and dozens of two[-year] carcinogenicity studies on multiple animal species, I can't conceive [of] that."[37]

Clinical Trial Presentation. Next, plaintiffs claim that there are inconsistencies in how pancreatic cancer events in Amylin's clinical trial data were

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[36] Fiorentino Study (Opp'n Ex. 7) at 148; *see also id.* at 144 ("no dysplastic lesions, pancreatic intraepithelial neoplasia (PanIN), or lesions resembling pancreatic cancer were observed in any pancreatic specimen examined at baseline or after treatment in either animal group").

[37] Goldkind 2015 Tr. (Ex. AG) at 112:20–113:1.

summarized in various documents. *See* Opp'n at 43–44. Plaintiffs do not dispute the critical issue: ***all*** clinical trial data were submitted to FDA, including ***all*** pancreatic events identified by plaintiffs. *Id.* at 43 (noting submission of "PBRER to the FDA"); *id.* at 44 ("researchers at Amylin submitted a journal article (which was later published and then submitted by Amylin to the FDA)"). This alone belies any argument that FDA was not "fully informed." Rather, plaintiffs are again quibbling with the significance of the evidence, not whether it was available to FDA. This is precisely the type of second guessing that preemption precludes.[38]

EXSCEL. The Exenatide Study of Cardiovascular Event Lowering Trial ("EXSCEL")—the largest RCT to date involving exenatide—was completed in 2017. This trial involved 14,752 patients who were followed up to maximum of 6.8 years after treatment with exenatide, and it specifically adjudicated pancreatic cancer as one

[38] Plaintiffs also blatantly misrepresent the facts, but are still unable to conjure up any newly acquired evidence. For example, plaintiffs argue (without citing any witness testimony) that there are "strikingly different results" reported between an internal summary and what Amylin included in a Periodic Benefit-Risk Evaluation Report (PBRER). Opp'n at 43–44. But these documents are analyzing two different data sets. Unlike the internal summary, the PBRER separates the data for Byetta (exenatide twice-daily) and Bydureon (exenatide once-weekly). And the total number of pancreatic cancer events for exenatide-treated subjects is the same in both documents: 4 patients. *Id.* Plaintiffs also argue that "researchers at Amylin" submitted a journal article in 2014 and "manipulated their selection of clinical trials" so that there would be "zero pancreatic cancers." *Id.* at 44. The article focused on 8 clinical trials and examined patient data for those treated for 24 or 30 weeks. *See* Opp'n Ex. 47 ("A pooled database of individual patient data from eight previously reported trials of exenatide QW was used to integrate safety data for 4,328 patients with type 2 diabetes treated for 24 or 30 weeks (blinded-comparator period)."). On its face, the article did not purport to include data from any other clinical trial. Plaintiffs claim that the article omitted a pancreatic cancer case, Opp'n at 44, but plaintiffs' "evidence" is the final clinical study report submitted to the FDA. In other words, the document they claim shows a pancreatic cancer event is the *same* document that plaintiffs admit the FDA received.

of its outcomes.[39] EXSCEL identified 31 pancreatic cancer events among those patients, but reported ***fewer*** events of pancreatic cancer in patients treated with exenatide compared to controls. That is, 16 patients taking a placebo developed pancreatic cancer, compared to 15 taking exenatide.[40]

As with the other clinical trial data, plaintiffs do not (and cannot) contend that Amylin failed to submit *all* EXSCEL data to FDA. Instead, plaintiffs argue, again without support, that EXSCEL was "the product of compromised data collection." Opp'n at 45. Regardless of the utter lack of basis for this accusation, this has nothing to do with the issue presented—whether the FDA had, and was "fully informed," of the results of EXSCEL.

Each of plaintiffs' arguments about EXSCEL are completely lawyer-manufactured for the purpose of responding to this motion, and should be rejected.[41] Indeed, none of plaintiffs' experts has identified any of these purported "data collection" issues. Rather, as is detailed in the defendants' *Daubert* motions, ***all*** of plaintiffs' experts ***avoided*** analyzing the EXSCEL trial, either because they never

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[39] Rury R. Holman, et al., *Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes*, N. Engl. J. Med. 377:1228 (Sept. 2017) (Ex. AP).

[40] Clinical Study Report, AMYLN06748007 at 183 (relevant portions attached as Ex. BD to Boehm Supp. Decl.).

[41] *Olivier v. Baca*, 913 F.3d 852, 861 (9th Cir. 2019) ("[L]egal memoranda … are not evidence, and do not create issues of fact capable of defeating an otherwise valid motion for summary judgment."); *Barcamerica Int'l USA Tr. v. Tyfield Imps., Inc.*, 289 F.3d 589, 593 n.4 (9th Cir. 2002) ("[T]he arguments and statements of counsel 'are not evidence and do not create issues of material fact.'"); *Todd v. Stryker Corp.*, 2012 WL 2922727, at *6 (E.D. Cal. May 1, 2012) ("[A]s many other courts have noted, counsel's bald advocacy about the significance of complex medical literature, unsupported by an admissible and sufficient expert opinion, cannot raise a genuine disputed fact issue.").

updated their reports after 2015[42]; or because they deliberately avoided discussing it, often at the instruction of counsel[43]; or in the case of Dr. Wells, because he realized that it was inconsistent with his litigation-driven general causation opinion and instead consistent with "no risk" of PDAC.[44]

Plaintiffs claim that the protocol for EXSCEL did not include the "adjudication of neoplasms" until 2011 or treat "pancreatic neoplasms" as "events of special interest" until October 2013. Opp'n at 45. This is irrelevant—these protocols were all submitted to FDA and *approved* by FDA.[45] And plaintiffs offer no evidence that any pancreatic cancer case was missed as a result of earlier protocols.

Plaintiffs also argue that some pancreatic cancer events counted in the placebo-arm were inconsistent with the EXSCEL protocol. For example, they identify three cases where a patient in EXSCEL was also taking sitagliptin. Opp'n at 46–47. Use of sitagliptin (or any other DPP-4 inhibitor) did not disqualify a patient from enrolling in the study.[46] To the contrary, taking a DPP-4 inhibitor was expressly ***allowed***: "concomitant use of DPP-4 inhibitors is permitted."[47] And once again, plaintiffs (1) offer only attorney argument, not expert analysis, in support; and (2) offer nothing "new" that was withheld from the FDA. For these reasons, plaintiffs' alleged inconsistencies are immaterial to a preemption analysis. If plaintiffs wanted to retain an expert to second-guess the EXSCEL trial's exclusion criteria they could have done

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[42] *See* Defs.' Mem. of Points & Authorities in Support of Mot. to Exclude Plaintiffs' Experts Drs. Betensky, Landolph, Woolf and Taylor at 1.

[43] *See* Defs.' Mem. of Points & Authorities in Support of Mot. to Exclude Plaintiffs' Experts Drs. Madigan, Wells, Brown and Gale at 19, 36, 38.

[44] *See id.* at 5, 14, 36.

[45] *See* AMYLN08149591 (attached as Ex. BE to Boehm Supp. Decl.).

[46] *See* AMYLN06748007 (Opp'n Ex. 53).

[47] AMYLN07832195 (relevant portions attached as Ex. BF to Boehm Supp. Decl.).

so, but they did not. Lay speculation by their attorneys in briefing is not evidence at all, let alone "newly acquired" evidence.[48]

Finally, to the extent plaintiffs do have relevant expert testimony, plaintiffs ignore it and argue the opposite. Plaintiffs assert that the "best number for EXSCEL" is not what was found in the clinical study report (15 events for exenatide and 16 events in placebo based on intention-to-treat), but is "12 exenatide versus 9 placebo" based on the "adjudicated pancreatic cancers per protocol" found in an appendix. Opp'n at 47. Again, plaintiffs concede that even their "12 exenatide versus 9 placebo" data was submitted to the FDA (and is not statistically significant), so this argument is irrelevant to a "newly acquired information" analysis. Opp'n at 47 (95% CI: 0.54, 3.06). Moreover, plaintiffs' argument is at odds with their experts' own testimony. Dr. Wells—the only plaintiffs' expert that actually reviewed EXSCEL clinical trial data—used the intention-to-treat data (15 exenatide/16 placebo). No expert in this litigation concludes otherwise. Indeed, both Dr. Wells and Dr. Madigan testified that the most appropriate way to analyze the clinical trial data is to use the intention-to-treat analysis, not the "per protocol" analysis.[49] According to Dr. Madigan, an intention-to-treat analysis includes "all patients who are randomized" to a treatment

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[48] Plaintiffs also argue, without any support, that Amylin did not "properly document and follow-up on" a particular case (No. [redacted]). Opp'n at 46. As plaintiffs acknowledge, the study report submitted to FDA advised that the patient had been lost to follow up and the study investigator was unable to obtain additional information. *Id.*; *see* AMYLN07208641 (Opp'n Ex. 51) at 8539. Again, this is a fact that the FDA was aware of, and plaintiffs do not (and cannot) point to anything more that should have been done under the study protocol. Nor do they present a qualified expert who supports this argument.

[49] Martin T. Wells Deposition Tr. (Jan. 22, 2020) at 127:22–128:21 (relevant portions attached as Ex. BG to Boehm Supp. Decl.); David Madigan, Ph.D. Deposition Tr. (Jan. 29, 2020) at 119:20–123:15 (relevant portions attached as Ex. BH to Boehm Supp. Decl.).

and had an adjudicated event occur.[50] In the words of Dr. Madigan, "if the patient's in, the patient's in. You count the events."[51] This is exactly what Amylin did.

C. Liraglutide (Victoza)

Plaintiffs focus on three pieces of data related to Victoza that they believe constitute "newly acquired information" that could support a CBE labeling change related to pancreatic cancer: (1) a single, benign pancreatic tumor reported in a Saxenda clinical trial,[52] (2) non-cancer-related findings from several animal experiments, and (3) a single observational study that evaluated the frequency of pancreatic cancer in a population of patients who ***did not*** take liraglutide.[53] Opp'n. at

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[50] Madigan 2020 Tr. (Ex. BH to Boehm Supp. Decl.) at 119:20–121:7; 122:9–22.

[51] Madigan 2020 Tr. (Ex. BH to Boehm Supp. Decl.) at 123:13–15.

[52] Plaintiffs claim that 2014 Saxenda Briefing Book submitted to FDA in advance of its approval was "scrubbed" by FDA from its website. Opp'n at 8. This is not true. The document is included in FDA's online archives available at: https://www.fda.gov/about-fda/about-website/fdagov-archive and searching for "Saxenda Endocrinologic and Metabolic Drugs Advisory Committee" (last accessed Sept. 3, 2020).

[53] Plaintiffs' reference to a statement by Novo's then-CMO, Dr. Alan Moses, Opp'n at 30–31, is both misleading and inaccurate. The statement does not suggest that Dr. Moses, or anyone else with Novo, believed that Victoza causes pancreatic cancer; nor does it suggest that Novo withheld any information from the FDA. As Dr. Moses explained, the statement was provided in an email response to a request for questions that could be asked by the committee members during the LEADER Advisory Committee meeting and, for which, the presenters wanted to make sure they had data available to fully and accurately respond. *See* Alan C. Moses, M.D. Deposition Tr. at 74:17–75:5 (relevant portions attached as Ex. BI to Boehm Supp. Decl.) [redacted]

28–35. As discussed below, these "new" data do not provide any evidence that could have supported a CBE-labeling change related to pancreatic cancer or altered the FDA's comprehensive analysis of this very issue.

Clinical Trial Adverse Events. Novo submitted all pancreatic cancer events from its clinical trials to the FDA as part of its regulatory submissions.[54] Although plaintiffs make vague claims about inconsistencies in how data were summarized in different documents,[55] *with one exception*, plaintiffs do not dispute that information about the pancreatic cancer events (both in the liraglutide and comparator groups) was provided to the FDA. Opp'n at 34–35.

[redacted]

[54] 2018 Liraglutide Periodic Safety Update Report (submitted to the FDA on Feb. 27, 2018), NNI-MDL_00476737 ("2018 PSUR") at 4 (relevant portions attached as Ex. BJ to Boehm Supp. Decl.).

[55] While plaintiffs suggest that there are inconsistencies between various data summaries created by Novo, all pancreatic events were submitted to the FDA in the PSUR data. Plaintiffs fail to acknowledge the context for each document is different, including that each was generated for a specific purpose and according to pre-specified inclusion and exclusion criteria. The 2018 PSUR includes all treatment-emergent events identified in completed clinical trials, 2018 PSUR (Ex. BJ to Boehm Supp. Decl.) at 142, while the 2017 internal "Safety Surveillance" summary provides information on all events from both ongoing and completed trials, regardless of whether those events were treatment-emergent or occurred long after treatment was stopped, NNI-MDL_02592351 (Opp'n Ex. 24) at 23. Application of these distinct criteria resulted in small differences in event counts between the two documents (4 versus 3 and 2 versus 1), but they did not alter the overall conclusion.

The one exception is a pseudopapillary tumor reported in study NN8022-1839, which plaintiffs allege was a pancreatic cancer that Novo "fail[ed] to report in its FDA submission." Opp'n at 9. This is not true. As a threshold matter, the tumor in question was ***not*** a pancreatic cancer—it was a rare, benign (non-malignant) tumor.[56] Further, Novo provided information about this event to the FDA on several occasions, including in the August 2015 PSUR (submitted to the FDA on September 8, 2015)[57] and in the final clinical trial report (which, paradoxically, plaintiffs reference in their Opposition Brief).[58]

Animal Experiments. Plaintiffs also point to five animal experiments—out of the thousands Novo conducted over the past two decades—they allege had adverse pancreatic findings which were not reported to the FDA. Opp'n at 28–32. As a threshold matter, none of the animals in these experiments were found to have pancreatic cancer or pre-cancerous lesions, despite often being treated with liraglutide doses well above those used in clinical practice.[59] *See infra* pp. 32–35. As such, these

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[56] The results of the biopsy in this case showed that the tumor was "negative for malignancy" and thus not a pancreatic cancer. Clinical Trial Report, SCALE – Obesity and Pre-diabetes (Jan. 18, 2016), NNI-MDL_01544708 ("SCALE CTR"), at 425 (relevant portions attached as Ex. BK to Boehm Supp. Decl.); Expert Report of Daniel O. Scharfstein, ScD (Dec. 16, 2019) at 11–12 (relevant portions attached as Ex. BL to Boehm Supp. Decl.).

[57] *See* 2014–2015 PSUR/PBER Submission Letter to FDA (Sept. 8, 2015), NNI-MDL_00068479 (attached as Ex. BM to Boehm Supp. Decl.).

[58] *See* SCALE CTR (Ex. BK to Boehm Supp. Decl.) at 425.

[59] Scientific Report (Oct. 5, 2001) (Opp'n Ex. 12) at 13 ("Histological findings in NN6622 and NN2211 combination study in ZDF rats: NN622/NN2211 decrease the relative beta-cell mass and induce focal pancreatic regeneration. NN622 alone increases the sporadic occurrence of acinar hyperplasia."); Study Report, NNI-MDL_00725778, "Effect of liraglutide on diabetic nephropathy in the db/db model" ("JYNR130201 Study Report") (attached as Ex. BN to Boehm Supp. Decl.); ADPC140901, NNI-MDL_00731756, "Effect of PYY analogue in combination with Liraglutide on glucose dynamics in sub-chronically dosed ZDF

experiments do not provide any evidence liraglutide causes or contributes to the development of pancreatic cancer in humans and do not constitute "newly acquired information" relevant to the pancreatic cancer issue.[60] To this point, it is telling that plaintiffs' own experts do not address any of these studies in their reports, nor do they rely on their findings as evidence relevant to the causation issue. Moreover, as discussed below, similar pancreatic findings were reported in other experiments and were considered by the FDA as part of its evaluation of the totality of the evidence on the pancreatic safety of incretin-based therapies (including pancreatic inflammation and acinar hyperplasia).[61]

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rats" ("ADPC140901 Protocol") (attached as Ex. BO to Boehm Supp. Decl.); NNI-MDL_0197007, "Effect of combination treatment with FGF21 and liraglutide on bone mineralization in DIO mice" ("KLyk131001 Study") (attached as Ex. BP to Boehm Supp. Decl.); Study Report, Liraglutide NNC 0090-0000-1170 (Jan. 2013) (Opp'n Ex. 18) ("The effect of liraglutide on pancreatic duct glands and stellate cells in chronically treated male and female ZDF rats.").

[60] Novo conducts thousands of animal studies with its different marketed and experimental medications. These studies are reported to the FDA as required under FDA guidelines. Indeed, FDA guidance makes clear the Agency wants manufacturers to use their judgment in submitting data from animal studies, limiting reports to animal findings "suggesting a significant risk in humans" and excluding those that are "too preliminary to interpret without replication or other investigation." *See* U.S. Dep't of Health & Human Servs., *Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies* (Dec. 2012), https://www.fda.gov/media/79394/download (relevant portions attached as Ex. BQ to Boehm Supp. Decl.). None of the findings discussed satisfy these criteria.

[61] Niels C. Nyborg, et al., *The Human GLP-1 Analog Liraglutide and the Pancreas: Evidence for the Absence of Structural Pancreatic Changes in Three Species*, Diabetes 61:5 at 1243–1249 (May 2012) (attached as Ex. BR to Boehm Supp. Decl.); Niels Vrang, et al., *The Effects of 13 wk of Liraglutide Treatment on Endocrine and Exocrine Pancreas in Male and Female ZDF Rats: A Quantitative and Qualitative Analysis Revealing No Evidence of Drug-Induced Pancreatitis*, Am. J. of Physiology, Endocrinology & Metabolism 303:2 at E253–E264 (May 15,

Below are brief summaries of each study identified by plaintiffs.

The 2001 ZDF Study. In the 2001 ZDF study, Opp'n at 28–29, Novo attempted to assess whether treating diabetic rats with a combination of two medications (liraglutide and an agent called NN622) could result in healthy regeneration (i.e., healing) of their pancreas.[62] No adverse pathologic changes were reported in animals treated with liraglutide, and none of the animals developed pancreatic cancer, pre-cancerous lesions, or pancreatitis.[63] While evidence of healthy regeneration was seen with combination therapy, no significant effect was observed with liraglutide alone, either in terms of regeneration or acinar hyperplasia.[64] Further, acinar hyperplasia[65] (on which plaintiffs seem to focus) is not a new finding. Minor increases in acinar cell size and number occasionally were observed in other animal studies involving incretins, including several of the toxicology studies conducted and

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2012) (attached as Ex. BS to Boehm Supp. Decl.); *see also* FDA Assessment (Ex. A).

[62] NNI-MDL_02599008 ("2001 ZDF Study") (Opp'n Ex. 12) at 7–8.

[63] *See* 2001 ZDF Study (Opp'n Ex. 12).

[64] *See id.* (Opp'n Ex. 12) at 17–18.

[65] Acinar hyperplasia means a benign increase in the size of normal, healthy acinar cells; it is not a pre-cancerous or a cancerous condition. Stanford Medicine, *Acinar Cell Nodule of the Pancreas* (original posting Jan. 9, 2008), http://surgpathcriteria.stanford.edu/pancreas/acinar_cell_nodule_pancreas/ (attached as Ex. BT to Boehm Supp. Decl.). In the study, acinar hyperplasia was observed in 1 of 19 animals treated with liraglutide alone. 2001 ZDF Study (Opp'n Ex. 12) at 26. This is not a new finding, as minor increases in acinar cell size and number occasionally were observed in other animal studies involving incretins, including several of the toxicology studies conducted and review by the FDA prior to the initial approval of Victoza and in one of the mice studies discussed by the FDA in its 2014 NEJM Assessment concluding that the totality of the evidence is "inconsistent" with a causal relationship between incretin-based therapies and pancreatic cancer. FDA Assessment (Ex. A) at 796.

review by the FDA prior to the initial approval of Victoza and in one of the mice studies discussed by the FDA in its 2014 NEJM Assessment.[66]

The 2012-2013 PDG Analysis. The PDG analysis, Opp'n at 28, 31–32, was a post-hoc, exploratory analysis which attempted to look at the effect of liraglutide on a normal compartment of the pancreas, known as pancreatic duct glands (PDGs).[67] As discussed in the 2015 briefing and in Defendants' opening brief, the analysis had significant methodologic problems which precluded forming any reliable conclusions about the effect of liraglutide on PDGs.[68] Regardless, there were no treatment-related adverse pancreatic effects observed in any of the animals receiving liraglutide.[69]

Plaintiffs' false allegation that Novo intentionally destroyed histology slides and other materials from this study also warrants a response. Opp'n at 29. While it is true that tissues and physical slides were discarded after several years of storage and associated degradation, nearly 2,000 high-resolution digital images reflecting all the pathology and staining were retained.[70] These digital images (rather than the slides) were used to conduct the original analysis; all of these images were provided to Plaintiffs' counsel on November 15, 2019.[71]

Studies JYNR130201 & KLyk131001. Unlike several other studies conducted by Novo, these experiments, Opp'n at 29–31, were not designed to assess the pancreatic safety of liraglutide and did not include systematic evaluation of pancreatic

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[66] FDA Assessment (Ex. A) at 796.

[67] Expert Report of Sarah Thayer, M.D., Ph.D. (Dec. 16, 2019) ("Thayer Report") at 21 (Ex. AT).

[68] *Id.* (Ex. AT).

[69] *Id.* (Ex. AT).

[70] *See* Declaration of Raymond M. Williams ("Williams Decl.") at ¶¶ 2–3.

[71] *Id.* ¶¶ 2–3.

tissue.[72] As such, the fact that two animals (one in each study) were observed to have an inflamed pancreas provides no reliable information about the pancreatic safety of the medication, and certainly does not suggest that liraglutide causes pancreatitis or pancreatic cancer. Indeed, it is well-recognized that there is a significant background rate of pancreatic findings in rodents, even when those animals are not exposed to any external agents or medications.[73]

Study ADPC140901. This study looked at the effect of combining a medication called a PYY analogue with liraglutide on glucose levels in ZDF rats.[74] [redacted][77]

[72] *See* JYNR130201 Study Report (Ex. BN to Boehm Supp. Decl.) at 10 (noting aim "[t]o evaluate the effect of liraglutide in prevention of diabetic nephropathy defined as reduction in albuminuria and mesangial expansion"); KLyk131001 Study (Ex. BP to Boehm Supp. Decl.) at 12 (noting aim of study was to "evaluate effects of treatment with combination of FGF21 and the GLP-1 agonist, liraglutide on body weight, body composition and on bone mineralization in DIO mice").

[73] Kristina D. Chadwick, et al., *Occurrence of Spontaneous Pancreatic Lesions in Normal and Diabetic Rats: A Potential Confounding Factor in the Nonclinical Assessment of GLP-1-Based Therapies*, Diabetes 63:1303 (Apr. 2014) (Ex. AU).

[74] ADPC140901 Protocol (Ex. BO to Boehm Supp. Decl.); *see also* NNI-MDL00731548 (Opp'n Ex. 15) at 2.

[75] NNI-MDL00731548 (Opp'n Ex. 15) at 2.

[76] *Id.* (Opp'n Ex. 15).

[77] *Id.* (Opp'n Ex. 15).

In sum, the 2001 ZDF study and the 2012 PDG analysis found no evidence of adverse pancreatic effects of liraglutide.[78] The sporadic pancreatic findings observed in the other three studies—even if related to liraglutide treatment (which they do not appear to be)—involve pancreatic inflammation (or pancreatitis), a potential side effect which already is warned about in the labeling for Victoza and all other incretin-based therapies.[79] Accordingly, none of these animal experiments provide any "newly acquired information" that could support a CBE labeling change related to pancreatic cancer. *See* 21 C.F.R. § 314.70(c)(6)(iii); *McGrath*, 393 F. Supp. 3d at 168; *Utts*, 251 F. Supp. 3d at 659–60.

The Humedica Study. Plaintiffs next turn to the Humedica study. Opp'n at 33–34. The Humedica study was an observational study which attempted to estimate the incidence of pancreatic cancer in a population of patients with type 2 diabetes and risk factors similar (at least only to some extent) to those in LEADER.[80] In addition to its numerous limitations, the study did not evaluate pancreatic cancer risk with liraglutide, ***as none of the subjects in the study actually took the medication***.[81] As such, the study does not provide any direct information regarding the risk of pancreatic cancer in patients taking liraglutide. Rather, it offers one estimate of the background rate of pancreatic cancer in a real-world population with type 2 diabetes—an estimate the study authors themselves cautioned was based on an approach that "resulted in notably lower malignancy rates [than other studies]," suggesting their analysis "may have less complete capture of malignancy diagnoses."[82]

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[78] *See supra* pp. 32–33.

[79] *See supra* pp. 33–35.

[80] Humedica Study Report (May 8, 2015), NNI-MDL_02111320 ("Humedica Study Report") (Opp'n Ex. 20) at 26.

[81] *Id.* (Opp'n Ex. 20) at 3–4.

[82] *Id.* (Opp'n Ex. 20) at 26.

With that background, we can turn to plaintiffs' claims regarding the study. *First*, plaintiffs allege that Novo "buried" the study data. Opp'n at 34. That is false. The study was publicly posted to the FDA's website, clinicaltrials.gov, in November 2015[83] and results are publicly available on Novo's website.[84]

Second, plaintiffs allege that Novo should have compared the incidence rate for pancreatic cancer observed in the liraglutide and placebo arms of the LEADER trial to the background rate estimate from Humedica. Opp'n at 32–34. But, even plaintiffs' own expert Dr. Madigan cautioned that comparing data from an observational study to the results from a closely monitored clinical trial is concerning and refused to draw inferences from the data.[85] The problem Dr. Madigan refers to—comparing data from two different studies to draw conclusions about causation—can be illustrated with an example. In the Humedica study, the background rate for pancreatic cancer was reported as 0.036 events per 100 patient years.[86] In 2019, Funch et al. published the results of an observational study evaluating the incidence of pancreatic cancer in

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[83] *See* https://clinicaltrials.gov/ct2/show/NCT02608853?term=Humedica+diabetes&draw=2&rank=1 (last visited Aug. 14, 2020).

[84] See Novo Nordisk Trials, *Estimation of Malignancy Rates within Humedica Patient Populations Sampled to be Representative of Liraglutide Initiators and LEADER™ Trial Participants*, https://www.novonordisk-trials.com/en/studie/?id=NN2211-4259&arrayList=NN2211-4259,NN2211-3784,NN2211-3577,NN2211-4118, NN2211-1436,NN2211-1499,NN2211-1644,NN2211-1800,NN2211-1698,NN2211-2063,NN2211-1636,NN2211-1464,NN2211-1692,NN2211-3962,NN2211-3917&Conditions=&AgeRanges=&Phases=&SearchTerm=NN2211-4259&Status=&Treatment=&AttachmentTypes=&country=&zip=.

[85] *See* Madigan 2020 Tr. (Ex. BH to Boehm Supp. Decl.) at 80:12–17, 198:4–201:17 ("There are concerns you have about such a comparison… So are there limitations with such comparisons? You betcha there are, and I'm not considering there are. I'm just observing, you know, how it turned out.").

[86] Humedica Study Report (Opp'n Ex. 20) at 6.

patients treated with liraglutide.[87] The incidence of pancreatic cancer events in patients taking liraglutide in that study was 0.021 events per 100 patient years.[88] A direct comparison of the results from these two observational studies would suggest that liraglutide reduced the risk of pancreatic cancer. Any conclusion drawn from such comparison would be no more reliable than those drawn from a comparison of Humedica and LEADER.

Third, plaintiffs take issue with the fact that Novo stated in the briefing document for the LEADER Advisory Committee meeting that the "predicted range for the background [rate of pancreatic cancer in a] T2DM population" was 0.05 – 0.08 events per 100 PYE, without mentioning the 0.036 number calculated in the Humedica analysis. Opp'n at 32–34. As an initial matter, Novo's decision to provide a reference range in its formal briefing book for the FDA based on data from three independent, peer-reviewed sources rather than its own internal analysis is entirely reasonable and appropriate. Moreover, Humedica notwithstanding, the incidence rate in LEADER falls within the expected background range as reported in the available literature.[89] Indeed, the incidence in the liraglutide arm of LEADER was in line with the placebo incidence rate in the Byetta EXSCEL trial (approximately 0.09 events per 100 PYE) and in the Januvia TECOS trial (0.07 events per 100 PYE).

In sum, none of the information plaintiffs claim Novo withheld from the FDA provides any evidence that Victoza causes pancreatic cancer, nor, for that matter, could support a CBE labeling change related to pancreatic cancer. Ultimately, no

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[87] *See* Donnie Funch, et al., *Liraglutide Use and Evaluation of Pancreatic Outcomes in a US Commercially Insured Population*, Diabetes Obes Metab. 2019:1–12 (attached as Ex. BU to Boehm Supp. Decl.).

[88] *Id.* (Ex. BU to Boehm Supp. Decl.) at 6.

[89] Thayer Report (Ex. AT) at 25–26. In fact, as plaintiffs acknowledge, the Humedica estimate falls squarely within the reference range provided in the 2018 PSUR (0.01–2.4 per 100 person years) provided to the FDA, which is based on a larger data set, including 14 independent, peer-reviewed sources.

amount of cherry-picking of study findings by plaintiffs' counsel, or allegations about what the FDA might do with some specific piece of data, can alter what the FDA has done and continues to do to this day. Considering the FDA's comprehensive review of the evidence over the past decade, its repeated conclusions about the absence of a causal relationship, and its labeling mandate under FDAAA, FDA would not approve a pancreatic cancer warning for Victoza or for any other incretin-based therapy.

CONCLUSION

For the reasons set forth above, plaintiffs' claims are preempted. First, adding a pancreatic cancer warning to the labeling of incretin-based therapies would "irreconcilably conflict" with the FDA's conclusion that such a warning is not substantiated by available scientific information. Second, plaintiffs do not identify "newly acquired information" that would satisfy regulatory requirements for submitting a proposed labeling change in the first place. Defendants respectfully request that this Court grant summary judgment on all counts on the basis of conflict preemption.

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Respectfully submitted,

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